

Pharmacologic treatment of pediatric obesity

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Abstract

Question There is a large population of overweight and obese children in my clinic. What medications for treatment of obesity are effective and can be used in children?

Answer Orlistat is the only medication indicated by the US Food and Drug Administration for the treatment of obesity in adolescents. It is approved by the Food and Drug Administration for use in adolescents aged 12 years and older. There is no single approach to successful treatment of obesity, and lifestyle modification should be maintained throughout the pharmacologic treatment.

Résumé

Question Dans ma pratique, il y a une grande population d'enfants obèses ou qui ont un excès de poids. Quels médicaments efficaces peut-on utiliser pour traiter l'obésité chez les enfants?

Réponse L'orlistat est le seul médicament indiqué par la Food and Drug Administration (FDA) des États-Unis pour le traitement de l'obésité chez l'adolescent. La FDA approuve l'utilisation de ce médicament pour les adolescents de 12 ans et plus. Il n'existe pas d'approche qui à elle seule permette de traiter avec succès l'obésité et il faut maintenir une stratégie de modification du mode de vie pendant tout le traitement pharmacologique.

The prevalence of weight problems in pediatric populations is increasing at an accelerated rate, and childhood obesity is one of the most critical public health concerns today. Recent estimates from the Canadian Community Health Survey have shown that 26% of Canadian children and adolescents are overweight or obese, compared with 15% in 1979.¹ Due to the increase of this epidemic there is an increased risk of future cardiovascular disease.

Metabolic consequences of pediatric obesity include atherogenic dyslipidemia (ie, elevated total cholesterol and low-density lipoproteins, decreased high-density lipoproteins, fatty streaks in the arteries), impaired glucose tolerance and insulin resistance, increased risk of type 2 diabetes, hypertension, metabolic syndrome, nonalcoholic steatohepatitis, coagulation abnormalities, and polycystic ovary syndrome.² In addition, excess body weight and hormonal imbalance during puberty have been associated with growth plate injuries, slipped capital femoral epiphysis, sleep apnea, and psychosocial problems that might ultimately lead to depression.^{3,4}

Treatment of obesity in children includes behavioural and dietary modifications, pharmacotherapy, and use of weight-loss supplements. Such patients should limit consumption of energy-dense, high-carbohydrate

beverages and snack foods high in sugar or fat; increase the time spent on physical activities and sports by at least 30 minutes daily; as well as limit exposure to television and video or computer games to no more than 1.5 hours a day.⁴ However, current dietary and behavioural methods for prevention of childhood obesity remain largely ineffective.

Pharmacologic interventions

Pharmacotherapy is an option available for extremely obese (ie, body mass index [BMI] ≥ 2 units above the 95th percentile) children older than 12 years of age who have not responded to 1-year dietary and lifestyle treatments, as well as for those with impaired glucose tolerance or insulin resistance, steatohepatitis, ovarian hyperandrogenism, or a strong family history of diabetes, myocardial infarction, or stroke.⁵ It has been demonstrated that a combination of medication and lifestyle modification decreases weight more than lifestyle change alone.⁶

Drugs approved by the Food and Drug Administration (FDA) to treat obese adults include phentermine, phendimetrazine, benzphetamine, diethylpropion (appetite suppressants), and orlistat (intestinal lipase inhibitor); however, most clinicians prescribe orlistat. Furthermore, only orlistat is indicated for the treatment of overweight adolescents. It is approved by the FDA for the treatment of obesity in adolescents aged 12 years and older.⁷ Until recently, sibutramine was widely used as an antiobesity medication;



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however, it has been pulled off of the market.⁸ Other weight-lowering drugs for teenagers and children should only be used in the context of a controlled clinical trial.

Orlistat

Orlistat acts by decreasing hydrolysis of ingested triglycerides and reducing gastrointestinal absorption of fat by approximately 30% via inhibition of intestinal lipases. Owing to its negligible absorption in the small intestine, orlistat is regarded as safe; however, unabsorbed fat excreted in feces can cause transient diarrhea, abdominal discomfort, and flatulence.⁵ Concomitant prescription of natural dietary fibres or a diet containing approximately 30% of calories from fat is recommended.⁹

When studied in children, orlistat decreased BMI by 0.5 to 4.2 kg/m² compared with either placebo or baseline (**Table 1**).¹⁰⁻¹⁴ Chanoine et al conducted a large multicentre, randomized, double-blind study with 539 obese adolescents aged 12 to 16 years at 32 centres in the United States and Canada.¹⁰ A 120-mg dose of orlistat (n=357) or placebo (n=182) was given 3 times daily for 1 year, along with a mildly hypocaloric diet, exercise, and behavioural therapy. Body mass index decreased in both groups up to week 12, thereafter increasing with placebo beyond the baseline. At the end of the study, BMI had decreased by 0.55 kg/m² with orlistat but increased by 0.31 kg/m² with placebo ($P=.001$). Mild to moderate gastrointestinal adverse events occurred in 9% to 50% of patients in the orlistat group and in 1% to 13% of patients in the placebo group.¹⁰ Eventually, the FDA approved orlistat for the treatment of obesity in adolescents aged 12 to 16 years old.

In one randomized controlled trial the difference in weight reduction between the orlistat and the placebo groups was considered clinically insignificant. This was despite a statistically significant difference in BMI before and after the study in the orlistat group (-1.3 [SD 1.6] kg/m², $P=.04$).¹² One systematic review reported a small mean BMI reduction (0.85 kg/m² for

orlistat) in obese adolescents on active medication combined with behavioural interventions.¹⁵

Orlistat should be considered first-line pharmacotherapy for adolescents with BMIs 2 or more units above the 95th percentile who continue to gain weight despite a 12-month trial of lifestyle modifications.⁵ The recommended dose is 120 mg with meals up to 3 times daily if the meal contains fat. The reduced absorption of fat-soluble vitamins, vitamin D in particular, observed with orlistat⁶ is of particular concern in the growing child. Therefore, the FDA recommends packaging of orlistat with a multivitamin containing 5000 IU of vitamin A, 400 IU of vitamin D, 300 IU of vitamin E, and 25 µg of vitamin K for adolescent use. Patients should be counseled to take orlistat and multivitamins at least 2 hours apart.⁷ Periodic health examinations during the therapy should include monitoring of weight, height, serum fat-soluble vitamin concentrations, and symptoms and signs of obesity-related comorbidities.⁵

Sibutramine

Sibutramine, a central serotonin and norepinephrine reuptake inhibitor, has been approved for treatment of obesity in adolescents aged 16 years or older.⁸ However, on October 8, 2010, the FDA asked the manufacturer to withdraw the medication from the market in the United States because of clinical data from the large Sibutramine Cardiovascular Outcomes (SCOUT) study that indicated increased risk of cardiovascular adverse events.¹⁶

The SCOUT trial was a randomized, double-blind, placebo-controlled, multicentre study including approximately 10 000 overweight men and women (aged ≥55 years, with BMI of 27 to 45 kg/m² or 25 to 27 kg/m² with an increased waist circumference) who had a history of cardiovascular disease (eg, coronary artery disease, stroke, occlusive peripheral arterial disease) or type 2 diabetes with at least one other cardiovascular risk factor. The study was conducted in Europe, Australia, and Latin America. Patients received either 10 mg of sibutramine daily or placebo, with a

Table 1. Clinical trials of orlistat in children

STUDY	DURATION	N	AGE	TYPE OF TRIAL	DOSE	BMI CHANGE
Chanoine et al, ¹⁰ 2005	12 mo	539	12-16 y	Randomized, double-blind, placebo-controlled	120 mg 3 times daily	-0.9 kg/m ² (vs placebo)
Ozkan et al, ¹¹ 2004	5-15 mo	42	10-16 y	Randomized, open-label, controlled	120 mg 3 times daily	-4.2 kg/m ² (vs control)
Maahs et al, ¹² 2006	6 mo	40	14-18 y	Randomized, double-blind, placebo-controlled	120 mg 3 times daily	-0.5 kg/m ² (vs placebo, non-significant)
McDuffie et al, ¹³ 2004	6 mo	20	12-17 y	Single group	120 mg 3 times daily	-2.0 kg/m ² (vs baseline)
Norgren et al, ¹⁴ 2003	3 mo	11	8-12 y	Single group	120 mg 3 or 4 times daily	-1.9 kg/m ² (vs baseline)

BMI—body mass index.

dose increase of 15 mg daily for subjects in the sibutramine group with inadequate weight loss. The study duration was 5 years, and the mean duration of treatment with sibutramine was about 3.5 years.

The difference in the change in body weight at the end of the study between placebo and sibutramine groups was small (2.5%). In addition, a 16% increase in the relative risk of cardiovascular adverse events (need for resuscitation, nonfatal stroke, nonfatal myocardial infarction, and cardiovascular death) was observed in the sibutramine group compared with placebo (hazard ratio 1.16; 95% confidence interval 1.03 to 1.31; $P=.02$). From the results of this study, the FDA concluded that the risk of cardiovascular adverse events from sibutramine outweighed the benefits from the resulting small weight loss. The manufacturer of sibutramine has voluntarily agreed to stop marketing the drug in the United States. The FDA recommends that health care professionals in the United States stop prescribing and dispensing sibutramine to patients, as well as contact patients and ask them to discontinue the medication.

Conclusion

Despite a substantial number of medications used for the treatment of obesity in adults, orlistat is the only drug indicated by the FDA for the treatment of overweight adolescents aged 12 years and older. Despite the benefits of the medication, lifestyle modification should be sustained throughout treatment. Further research is needed in order to optimize clinical approaches for prevention, screening, and pharmacologic treatment of pediatric weight problems.

Competing interests

None declared

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